12-18-00 JC02 Rec'd PCT/PTO 15 DEC 2000 PCT



FORM PTO-1390 (REV 10-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 12964.19

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/719946

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/DE99/01844 | 24 June 1999 | 26 June 1998 |

TITLE OF INVENTION: MEDICAMENTS CONTAINING BISPHOSPHONIC ACIDS AND DERIVATIVES THEREOF WHICH ARE PROVIDED FOR PREVENTING AND TREATING AUTOIMMUNE DISEASES AND ALLERGIES

APPLICANT(S) FOR DO/EO/US: JOMAA, Hassan

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)
4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11 to 16 below concern document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: Postcard and Express Mail Certificate

| 17. ☒ The following fees are submitted: | CALCULATIONS PTO USE ONLY | |
|---|---|---|
| **BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5) ) :** | | |
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... $1000.00 | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... $860.00 | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... $710.00 | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $690.00 | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $100.00 | | |
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | $ 860.00 | |
| Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ .00 | |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total claims | 9 - 20 = | | X $18.00 | $ .00 | |
| Independent claims | 1 - 3 = | | X $80.00 | $ .00 | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | + $270.00 | $ 270.00 | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $ 1130.00 | |
| ☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. | | | | $ 565.00 | |
| **SUBTOTAL =** | | | | $ 565.00 | |
| Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | | + | $ | |
| **TOTAL NATIONAL FEE =** | | | | $ 565.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property | | | + | $ | |
| **TOTAL FEES ENCLOSED =** | | | | $ 565.00 | |
| | | | | Amount to be refunded: | $ |
| | | | | charged: | $ |

a. ☒ A check in the amount of $ 565.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-1394. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:
Warren B. Kice
Haynes and Boone, L.L.P.
901 Main Street, Suite 3100
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SIGNATURE:

Warren B. Kice
NAME

22,732
REGISTRATION NUMBER

| U.S. APPLICATION NO. (if known, see 37 CFR 1.5) | INTERNATIONAL APPLICATION NO. | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/ 19946 | PCT/DE99/01844 | 12964.19 |

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| Total claims | 9 - 20 = | | X $18.00 | $ .00 | |
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SIGNATURE:
Warren B. Kice

NAME
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REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



| | | |
|---|---|---|
| In re application of: JOMMA, Hassan | § | |
| Serial No.: US National Phase of PCT/DE99/01844 | § | Group Art Unit: Unknown |
| Filed: Herewith | § | Examiner: Unknown |
| For: MEDICAMENTS CONTAINING BISPHOSPHONIC ACIDS AND DERIVATIVES THEREOF WHICH ARE PROVIDED FOR PREVENTING AND TREATING AUTOIMMUNE DISEASES AND ALLERGIES | § | |

ATTN: DO/EO/US
Commissioner For Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to the initial examination of the above-identified application, please amend the application as follows:

IN THE CLAIMS:

Attached are substitute Claims 1 through 6 as amended in the Patent Cooperation Treaty under Article 34.

REMARKS

Claims 1 through 6 have been amended. The filing fee has been calculated according to the above amendments.

Should the Examiner have any questions or comments regarding the amendments, the Examiner may telephone the undersigned at the number listed below.

Respectfully submitted,

Warren B. Kice
Registration No. 22,732

Dated: 12/15/00

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File: 12964.19
D-849365.1

Field of the invention

This invention relates to pharmaceutical preparations for the prevention and treatment of autoimmune disorders and of allergies.

It is known that autoimmune disorders, such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, uveitis *etc.*, and allergies, in particular food allergies, nickel allergy and pollen allergies *etc.* are attributable to an inappropriate reaction by the body's immune system.

It is furthermore known that, due these inappropriate reactions of the immune system, endogenous substances (autoantigens) are perceived as foreign substances and a defence reaction develops against them which results in damage to the body's own tissue. Depending upon the organ system involved, some 40 autoimmune conditions have been identified. These defence reactions may be directed both against individual cell constituents and against entire cells or organs.

Allergies are known to be the result of hypersensitivity towards certain substances, the allergens, which gives rise to an over-reaction of the immune system. In other words, affected subjects react to certain substances (the

allergens) with specific symptoms as a defence against the allergen.

Prior art

Attempts to treat autoimmune disorders caused by inappropriate reactions of the immune system with non-specifically acting immunosuppressants have proved entirely unsatisfactory as the use of immunosuppressants brings about a general inhibition of inflammatory reactions which may go as far as to shut down large parts of the immune system, so resulting in the occurrence of many side-effects, for example toxic damage, increased susceptibility to infectious diseases and increased risk of the occurrence of malignant diseases.

The alternative approach of avoiding the side-effects associated with the use of non-specifically acting immunosuppressants by using selective suppression (*c.f. Ann. Neurol.* 37 Suppl. 1, 87-101), with action being purposefully and specifically taken against the allergens or autoantigens at various points in the defence reaction, also met with less than complete success.

One of these methods is based upon the oral or inhalatory administration of autoantigens or allergens specific to the particular disorder. While it is indeed possible in this manner to reinduce the body's resistance to these autoantigens or allergens or to enable the body to tolerate the autoantigens or allergens which have hitherto been attacked and initiate the enhanced immune response, the overall success rate of this patient desensitisation is limited because the desensitisation is inadequate (*Ann. N. Y. Acad. Sci.* 778, 1-27; *Ann. N. Y.*

*Acad. Sci.* 778, 243-250; *Science* 261, 1727-1730; *Annu. Rev. Med.* 48, 341-351).

The mechanism of oral reinduction of tolerance by these substances is not yet completely understood. It may, however, be assumed that in the case of oral administration a part is played both by the immune system and by the bacterial flora of the gastrointestinal tract, the T cells (T lymphocytes), in particular the γδ-T cells (*The Journal of Immunology* 158, 3610-3618; *Res. Immunol.* 147, 49-59; *Immunology Letters* 48, 97-102).

It was, however, entirely surprising that the reinduction of tolerance achieved with oral or inhalatory administration of autoantigens or allergens specific to the disorder was greatly promoted if the autoantigens or allergens were administered in combination with bisphosphonic acids or the derivatives thereof. These combinations may thus successfully be used for the prevention and treatment of autoimmune disorders or allergies.

The use of bisphosphonic acids and of some of the derivatives thereof in pharmaceutical preparations is already known. The microbiostatic action of bisphosphonic acids (DE 3611522), the action thereof in the treatment of disorders of calcium and phosphate metabolism (DE 2534390, DE 2534391, DE 3334211, DE 3434667, DE 2745083), cytostatic action (DE 3425812), the lipid-reducing action thereof (*Arzneimittelforschung* 46, 759-762) and the ability thereof to stimulate immune cells (WO 97/38696 A1) are already known. The fact that bisphosphonic acids have an immunomodulatory action (WO 97/38696 A1) is furthermore known and has been used.

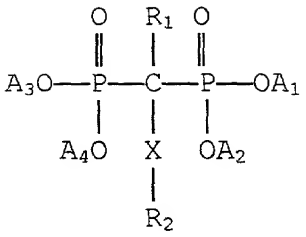
However, use of these compounds is associated with many side-effects which are determined by the mode of administration. In the case of intravenous infusion, such side-effects are fever, flu-like symptoms with violent shivering, lymphopenia and thrombocytopenia and, in the case of oral administration, they are painful swallowing, oesophagitis, oesophageal erosion, oesophageal ulceration, dyspepsia, diarrhoea *etc.*. Moreover, oral treatment with bisphosphonates, for example, requires relatively large quantities of active substance and therapeutic success is still unsatisfactory (*Drug-Saf.* 14, 158-170).

It was thus not in the least obvious to use this group of compounds in combination with autoantigens or allergens in order to reinduce the body's tolerance to autoantigens or allergens.

Description of the invention

The invention accordingly relates to a novel method of solving the hitherto unsolved problem of the prevention and treatment of autoimmune disorders and of allergies by means of pharmaceutical preparations, namely to use the autoantigens or allergens hitherto used to treat autoimmune disorders and allergies in combination with bisphosphonates or the derivatives thereof.

The invention relates to the use of bisphosphonic acids and the derivatives thereof for the production of pharmaceutical preparations for the prevention and treatment of autoimmune diseases or allergies, wherein the bisphosphonic acids and the derivatives thereof which are used are those of the general formula:



(I),

in which

$A_1$, $A_2$, $A_3$, $A_4$, which may be identical or different and mean hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

X, which may also be absent or may be alkylene, alkenylene or hydroxyalkylene,

$R_1$, $R_2$, which may be identical or different and mean H, OH, $-NH_2$, a substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heterocyclic residue or $-SR_3$, Cl and $-NR_3R_4$, in which

$R_3$, $R_4$, which may be identical or different and mean H, OH, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue,

and the pharmaceutically compatible salts, esters thereof as well as salts of esters or compounds which, on administration, form the compounds to be administered as metabolites or catabolites, in combination with the specific autoantigens for the prevention and treatment of the particular autoimmune disorder, or in combination with the specific allergens for the prevention and treatment of the particular allergy, wherein, instead of the particular autoantigens or allergens, it is also possible to use fragments or derivatives thereof and the analogues or fragments thereof of the autoantigens or allergens, providing that these each exhibit the same immunological characteristics as the corresponding whole molecules, and

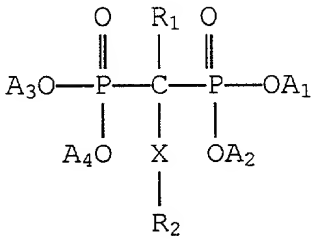
wherein the bisphosphonic acids or the derivatives thereof and the autoantigens or allergens or fragments, derivatives or analogues thereof

may be administered simultaneously or in succession.

The substances may here be administered both synchronously and with a delay by simultaneous or separate administration of the active substances.

From the group of bisphosphonic acids and the derivatives thereof of the general formula I, those bisphosphonic acids and the derivatives thereof which are preferred for

use for the prevention and treatment of autoimmune disorders or allergies are of the general formula:



(II),

in which

$A_1$, $A_2$, $A_3$, $A_4$, which may be identical or different and mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, an aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

$R_1$, means H, OH, $NH_2$,

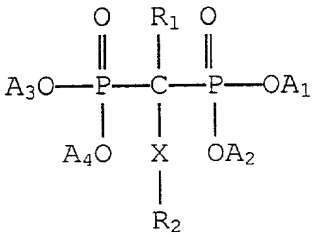
X, which may also be absent or may be alkylene, alkenylene or hydroxyalkylene, in each case having 1 to 12 carbon atoms,

$R_2$, means H, OH, $-NH_2$, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted

by functional groups, or $-SR_3$, Cl and $-NR_3R_4$, in which

$R_3$, $R_4$, which may be identical or different and mean H, OH, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups.

Bisphosphonic acids and the derivatives thereof which have proved particularly effective are those of the general formula:



(III),

in which

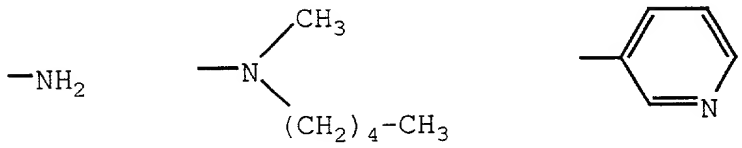
$A_1$, $A_2$, $A_3$, $A_4$, which may be identical or different and mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or

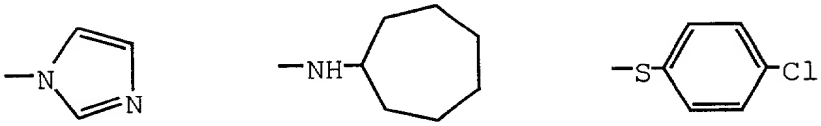
ammonium compounds derived from ethylenediamine or amino acids,

$R_1$, means H, OH,

X, which may also be absent or may mean $(CH_2)_{1-5}$, amidino,

$R_2$, may mean





Some examples of these are:

aminohydroxymethylidenebisphosphonic acid (AMP),
2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid (AEP),
3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronic acid),
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid),
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (AHP),
amidinomethylenebisphosphonic acid (AIMP),
3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid (ibandronic acid),
2-(3-pyridinyl)-1-hydroxyethylidenebisphosphonic acid (risedronic acid),
1-hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid (zoledronic acid),
cycloheptylaminomethylenediphosphonic acid (cimadronic acid),

4-chlorophenylthiomethylene-1,1-bisphosphonic acid
(tiludronic acid)
and the derivatives thereof.

Autoimmune disorders and allergies are prevented and treated by combined use of a bisphosphonic acid or the derivatives thereof and an autoantigen which initiates the particular autoimmune disorder, such as for example in

| | |
|---|---|
| multiple sclerosis | with myelin basic protein (MBP), further extracts from nervous system tissue, |
| rheumatoid arthritis | with type I, II or III collagen, |
| Hashimoto thyroiditis | with thyroglobulin, |
| myasthenia gravis | with acetylcholine receptor protein, |
| lupus erythematosus | with DNA, |
| diabetes mellitus | with islet cell extracts, human insulin, |
| primary biliary cirrhosis | with liver extracts, |
| active chronic hepatitis | with liver cell extracts, |
| adrenalitis/Addison's disease | with adrenal cortex extracts, |
| polymyositis | with skin extracts, muscle extracts, |
| dermatomyositis | with muscle and/or skin extracts, |
| autoimmune haemolytic anaemia | with haemopoetic cell line extracts, |
| myocarditis<br>myopericarditis | with heart extracts, |
| scleroderma | with skin extracts, skin cell extracts, |

| | |
|---|---|
| uveitis (phacouveitis, sympathetic ophthalmia) | with eye lens proteins, S-antigens, S-antigen mixtures, |
| pemphigus vulgaris | with skin extracts, |
| pemphigoid | with skin extracts, |
| pernicious anaemia | with gastric cell extracts, parietal cell extracts, intrinsic factor, |
| autoimmune atrophic gastritis | with gastric cell extracts, |
| Crohn's disease | with intestinal extracts, |
| colitis ulcerosa | with intestinal extracts |
| or in allergies | with the allergy-specific allergens. |

Combined use is also taken to include cases in which autoantigens or allergens are already present. Such cases include, for example, Crohn's disease, in which the autoantigen is already present in the intestine as a result of the disease. In this case, in the event of oral or rectal administration, only the bisphosphonic acids or the derivatives thereof need be administered. It is also unnecessary to administer the allergen if, during treatment, the affected subject is in an environment in which the allergy-specific allergen is already present (for example pollen during the pollen release season).

Combined use may proceed not only by oral administration, for example by means of tablets *etc.*, but also, for example, by rectal, inhalatory administration, by application onto the skin or mucous membranes. Preferred administration forms are oral and inhalatory administration and application onto the skin or mucous membranes.

Of these administration forms, inhalation has proved to be particularly gentle because elevated activity is achieved with only very small quantities of autoantigen or allergen and bisphosphonic acid or the derivatives thereof and any possible side-effects of the active substances may accordingly be minimised.

The bisphosphonic acids and the derivatives thereof which are preferably used are those which are poorly resorbed, which include, for example, aminobisphosphonic acids and the derivatives thereof.

Preferred pharmaceutical compositions are tablets, sugar-coated pills, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, sugar-coated pills, capsules, pills and granules may contain, apart from the active substances, conventional excipients, such as (a) fillers and extenders, for example starch, lactose, cane sugar, glucose, mannitol and silica, (b) binders, for example carboxymethyl-cellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) suspending agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) dissolution retardants, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorbents, for example kaolin and bentonite and (i) lubricants, for example talcum, calcium and magnesium stearate and solid polyethylene glycols or mixtures of the substances stated in (a) to (i).

The tablets, sugar-coated pills, capsules, pills and granules may be provided with conventional coatings and shells, which optionally contain opacifying agents, and may be of a composition such that they release the active substance, optionally with a delay, solely or preferentially in a specific part of the intestinal tract, wherein polymeric substances and waxes may, for example, be used as matrix materials.

The active substance or substances, optionally together with one or more of the above-stated excipients, may also assume microencapsulated form.

Apart from the active substance or substances, suppositories may contain conventional water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cocoa fat and higher esters (for example $C_{14}$ alcohol with $C_{16}$ fatty acid) or mixtures of these substances.

Apart from the active substance or substances, ointments, pastes, creams and gels may contain conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth gum, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talcum and zinc oxide or mixtures of these substances.

Apart from the active substance or substances, powders and sprays may contain conventional excipients, for example lactose, talcum, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain conventional propellants, for example chlorofluoro-carbons.

Apart from the active substance or substances, solutions and emulsions may contain conventional excipients, such as solvents, solubilising agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, peanut oil, maize oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and sorbitan fatty acid esters or mixtures of these substances.

Apart from the active substance or substances, suspensions may contain conventional excipients, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth gum or mixtures of these substances.

The stated formulation forms may also contain colorants, preservatives as well as with odour- and flavour-enhancing additives, for example peppermint oil and eucalyptus oil and sweeteners, for example saccharin.

Bisphosphonic acids or the derivatives thereof of the formula (I) are suitable for simultaneous, separate or temporally staged use with the autoantigens or allergens, and these compounds should accordingly be present in the pharmaceutical preparations listed above, preferably in a concentration of approx. 0.1 to 99.5 wt.%, relative to the complete mixture. The concentration of the

autoantigens or allergens should be 0.1 to 99.5 wt.% in this case too.

Apart from the compounds of the formula (I) and the autoantigen or allergen, the pharmaceutical preparations listed above may also contain further pharmaceutical active substances.

The pharmaceutical preparations listed above are produced in the conventional manner using known methods, for example by mixing the active substance or substances with the excipient or excipients.

The stated preparations may be administered to humans or animals orally, rectally, intravaginally, topically (powders, ointments, drops) and in cavities and body cavities. Suitable preparations for oral treatment which may be considered are solutions and suspensions, gels, infusion formulations, emulsions, ointments or drops. Topical treatment may be performed using ophthalmological and dermatological formulations, silver and other salts, ear drops, eye ointments, powders or solutions. For animals, administration may be made by suitable formulation with feed or drinking water. Gels, pulverulent formulations, powders, tablets, delayed-release tablets, premixes, concentrates, granules, pellets, boli, capsules, aerosols, sprays, inhalatory preparations may also be used in humans and animals. The compounds according to the invention may furthermore be incorporated into other support materials, such as for example plastics (plastic chains for topical treatment), collagen or bone cement.

The quantities of the individual derivatives required to achieve the desired effect vary very widely. In general, it has proved advantageous in both human and veterinary medicine to administer the active substance or substances of the formula (I) in total quantities of approx. 0.5 to approx. 2000 mg per 24 hours, optionally in the form of two or more individual doses, in order to achieve the desired results. An individual dose preferably contains the active substance or substances in quantities of approx. 0.5 to approx. 2000 mg. It may, however, be necessary to deviate from the stated dosages, specifically as a function of the species and body weight of the subject to be treated, the nature and severity of the condition, the nature of the preparation and administration of the pharmaceutical preparation and the period of time or interval within which the preparation is administered.

It may accordingly be sufficient in some cases to use less than the above-stated quantity of active substance, while in other cases the active substance must be used in a quantity greater than that stated above. The person skilled in the art will establish the optimum dosage and mode of administration of the active substances in each case on the basis of his/her expertise.

When treating animals, the compounds to be used according to the invention may be given in the conventional concentrations and preparations together with feed or with feed preparations or with drinking water.

Examples

Tablets are produced in a manner known *per se* using a mixture of

| | | | |
|---|---|---|---|
| 1. | 3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt | 600 | mg |
| | Bovine collagen, type II | 10 | mg |
| | Mannitol | 400 | mg |
| | Starch | 50 | mg |
| | Magnesium stearate | 10 | mg |
| 2. | 4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$ | 26 | mg |
| | Bovine collagen, type II | 10 | mg |
| | Mannitol | 400 | mg |
| | Starch | 50 | mg |
| | Magnesium stearate | 10 | mg |
| 3. | 3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$ | 1.125 | mg |
| | Bovine collagen, type II | 10 | mg |
| | Mannitol | 400 | mg |
| | Starch | 50 | mg |
| | Magnesium stearate | 10 | mg |
| 4. | 3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt | 600 | mg |
| | Myelin basic protein (MBP) | 8 | mg |
| | Mannitol | 400 | mg |
| | Starch | 50 | mg |
| | Magnesium stearate | 10 | mg |

| | | | |
|---|---|---|---|
| 5. | 4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$ | 26 | mg |
| | Myelin basic protein (MBP) | 8 | mg |
| | Mannitol | 400 | mg |
| | Starch | 50 | mg |
| | Magnesium stearate | 10 | mg |
| 6. | 3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$ | 1.125 | mg |
| | Myelin basic protein (MBP) | 8 | mg |
| | Mannitol | 400 | mg |
| | Starch | 50 | mg |
| | Magnesium stearate | 10 | mg |

Capsules are produced in a manner known *per se* using

| | | | |
|---|---|---|---|
| 7. | 3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt | 600 | mg |
| | Myelin basic protein (MBP) | 8 | mg |
| | Proteolipid protein | 15 | mg |
| | Magnesium stearate | 15 | mg |
| 8. | 4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$ | 26 | mg |
| | Myelin basic protein (MBP) | 8 | mg |
| | Proteolipid protein | 15 | mg |
| | Magnesium stearate | 15 | mg |

| | | | |
|---|---|---|---|
| 9. | 3-Methylpentylamino-1-hydroxypropyl-idene-1,1-bisphosphonate, monosodium salt, $1H_2O$ | 1.125 | mg |
| | Myelin basic protein (MBP) | 8 | mg |
| | Proteolipid protein | 15 | mg |
| | Magnesium stearate | 15 | mg |
| 10. | 3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt | 600 | mg |
| | Bovine collagen, type II | 10 | mg |
| | Magnesium stearate | 15 | mg |
| 11. | 4-Amino-1-hydroxypropylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$ | 26 | mg |
| | Bovine collagen, type II | 10 | mg |
| | Magnesium stearate | 15 | mg |
| 12. | 3-Methylpentylamino-1-hydroxypropyl-idene-1,1-bisphosphonate, monosodium salt, $1H_2O$ | 1.125 | mg |
| | Bovine collagen, type II | 10 | mg |
| | Magnesium stearate | 15 | mg |

wherein the above constituents are mixed together and then introduced in conventional manner into a hard gelatine capsule.

A preparation for inhalation for a 2 ml dose is produced using:

| | | | |
|---|---|---|---|
| 13. | 4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$ | 1.3 | mg |
| | Myelin basic protein | 15 | mg |
| | β-Cyclodextrin hydrate | 7 | mg |
| | pH 7.2 phosphate buffer | 0.2 | ml |
| | water for injection; | | |
| 14. | 3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt | 30 | mg |
| | Myelin basic protein | 15 | mg |
| | β-Cyclodextrin hydrate | 7 | mg |
| | pH 7.2 phosphate buffer | 0.2 | ml |
| | water for injection; | | |
| 15. | 3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$ | 0.25 | mg |
| | Myelin basic protein | 15 | mg |
| | β-Cyclodextrin hydrate | 7 | mg |
| | pH 7.2 phosphate buffer | 0.2 | ml |
| | water for injection; | | |
| 16. | 4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$ | 1.3 | mg |
| | Bovine collagen, type II | 10 | mg |
| | β-Cyclodextrin hydrate | 7 | mg |
| | pH 7.2 phosphate buffer | 0.2 | ml |
| | water for injection; | | |

| | | | |
|---|---|---|---|
| 17. | 3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt | 30 | mg |
| | Bovine collagen, type II | 10 | mg |
| | β-Cyclodextrin hydrate | 7 | mg |
| | pH 7.2 phosphate buffer | 0.2 | ml |
| | water for injection; | | |
| 18. | 3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$ | 0.25 | mg |
| | Bovine collagen, type II | 10 | mg |
| | β-Cyclodextrin hydrate | 7 | mg |
| | pH 7.2 phosphate buffer | 0.2 | ml |
| | water for injection. | | |

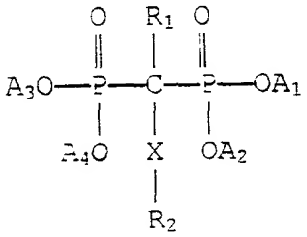
The bisphosphonate (for example alendronate) and the autoantigen (for example MBP) are dissolved in a phosphate buffer solution and the β-cyclodextrin hydrate is dissolved therein. The solution is made up to the desired volume with water for injection, sterilised by filtration and aseptically packaged in containers suitable for inhalation by atomisation.

**AMENDED CLAIMS**

Claims

1. Use of bisphosphonic acids and the derivatives thereof for the production of pharmaceutical preparations for prevention and/or treatment of autoimmune diseases and/or allergies, characterised in that as bisphosphonic acids and derivatives thereof are used:

   - Bisphosphonic acids and their derivatives of the general formula:



   are used, in which

   $A_1$, $A_2$, $A_3$, $A_4$, which may be identical or different, may mean hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylene diamine or amino acids,

   X, which may also be absent, may mean alkylene alkenylene or hydroxyalkylene,

   $R_1$, $R_2$, which may be identical or different, may mean H, OH, $NH_2$, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heterocyclic residue and further $-SR_3$, Cl and $-NR_3R_4$, in which

$R_3$, $R_4$, which may be identical or different, may mean H, OH, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue,

- and or their pharmaceutically compatible salts, esters thereof as well as salts of esters
- and/or compounds which, on administration, form the compounds to be administered as metabolites or catabolites,

wherein the bisphosphonic acids and/or their derivatives and/or the compounds which on administration form the suitable metabolites or catabolites which correspond to the above bisphosphonic acids and their derivatives are used in combination with the specific autoantigens for the prevention and treatment of the particular autoimmune disorder, or
in combination with the specific allergens for the prevention and treatment of the particular allergy, wherein, instead of the particular autoantigens or allergens, wherein it is also possible to use fragments or derivatives thereof and the analogues and fragments thereof of the autoantigens or allergens instead of the autoantigens or allergenes, providing that the mentioned substances respectively exhibit the same immunological characteristics as the corresponding whole molecules.

2. Use of bisphosphonic acids as well as their derivatives according to claim 1, characterised in that, in the general formula (I)

$A_1$, $A_2$, $A_3$, $A_4$, which may be identical or different, may mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a

heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylene diamine or amino acids,

$R_1$, may mean H, OH, $NH_2$,

X, which may also be absent, may mean alkylene, alkenylene or hydroxyalkylene, in each case having 1 to 12 carbon atoms,

$R_2$, may mean H, OH, $NH_2$, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may be substituted by functional groups, or furthermore $-SR_3$, Cl and $-Nr_3R_4$, in which

$R_3$, $R_4$, which may be identical or different, may mean H, OH, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may be substituted by functional groups.

3. Use of bisphosphonic acids as well as their derivatives according to claim 1, characterised in that, in general formula (I)

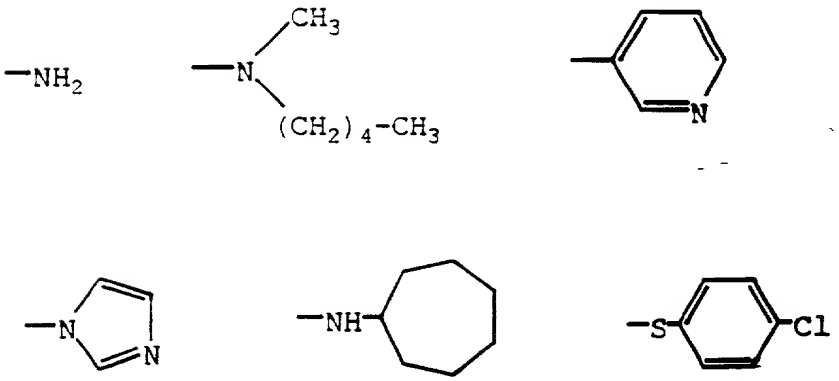
$A_1$, $A_2$, $A_3$, $A_4$, which may be identical or different may mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these

residues may be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca. Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylene diamine or amino acids,

$R_1$, may mean H, OH,

X, which may also be absent, may mean $(CH_2)_{1-5}$, amino,

$R_2$ may mean



4. Use of bisphosphonic acids and the derivatives thereof in combination with autoantigens or allergens for the production of pharmaceutical preparations for the prevention and/or treatment of autoimmune conditions and/or allergies according to claim 1 to 3, characterised in that the following are used for the treatment of

| | |
|---|---|
| multiple sclerosis | myelin basic protein (MBP), further extracts from nervous system tissue, |
| rheumatoid arthritis | type I, II or III collagen, |
| Hashimoto thyroiditis | thyroglobulin, |
| myasthenia gravis | acetylcholine receptor protein, |
| lupus erythematosus | DNA, |
| diabetes mellitus | islet cell extracts, human insulin, |
| primary biliary cirrhosis | liver extracts, |

| | |
|---|---|
| active chronic hepatitis | liver cell extracts, |
| adrenalitis/Addison's disease | adrenal cortex extracts, |
| polymyositis | skin extracts, muscle extracts, |
| dermatomyositis | muscle and/or skin extracts, |
| autoimmune haemolytic anaemia | haemopoetic cell line extracts, |
| myocarditis myopericarditis | heart extracts, |
| scleroderma | skin extracts, skin cell extracts, |
| uveitis (phacouveitis, sympathetic ophtalmia) | eye lens proteins, S-antigens, S-antigen mixtures, |
| pemphigus vulgaris | skin extracts, |
| pemphigoid | skin extracts, |
| pernicious anaemia | gastric cell extracts, parietal cell extracts, intrinsic factor, |
| autoimmune atrophic gastritis | gastric cell extracts, |
| Crohn's disease | intestinal extracts, |
| colitis ulcerosa | intestinal extracts |
| allergies | allery-specific allergens. |

5. Use of bisphosphonic acids and the derivatives thereof for the productions of pharmaceutical preparations for the prevention and/or treatment of autoimmune conditions and/or allergies according to claim 1 to 3, characterised in that the combination preparations are administered in solid form, as ointments, as solutions or as sprays.

PTO/SB/103 (8-96)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE


# Declaration and Power of Attorney for Patent Application
# Erklärung für Patentanmeldungen mit Vollmacht

## German Language Declaration

Als nachstehend benannter Erfinder erkläre ich hiermit an Eides Statt:

daß mein Wohnsitz, meine Postanschrift und meine Staatsangehörigkeit den im nachstehenden nach meinem Namen aufgeführten Angaben entsprechen, daß ich nach bestem Wissen der ursprüngliche, erste und alleinige Erfinder (falls nachstehend nur ein Name angegeben ist) oder ein ursprünglicher, erster und Miterfinder (falls nachstehend mehrere Namen aufgeführt sind) des Gegenstandes bin, für den dieser Antrag gestellt wird und für den ein Patent für die Erfindung mit folgendem Titel beantragt wird:

_____

_____

deren Beschreibung hier beigefügt ist, es sei denn (in diesem Falle Zutreffendes bitte ankreuzen), diese Erfindung

☐ wurde angemeldet am _____ unter der US-Anmeldenummer oder unter der Internationalen Anmeldenummer im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebier des Patentwesens (PCT) _____ und am _____ abgeändert (falls zutreffend).

Ich bestätige hiermit, daß ich den Inhalt der oben angegebenen Patentanmeldung, einschließlich der Ansprüche, die eventuell durch einen oben erwähnten Zusatzantrag abgeändert wurde, durchgesehen und verstanden habe.

Ich erkenne meine Pflicht zur Offenbarung jeglicher Informationen an, die zur Prüfung der Patentfähigkeit in Einklang mit Titel 37, Code of Federal Regulations, § 1.56 von Belang sind.

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**MEDICAMENTS CONTAINING BISPHOSPHONIC ACIDS AND DERIVATIVES THEREOF WHICH ARE PROVIDED FOR PREVENTING AND TREATING AUTOIMMUNE DISEASES AND ALLERGIES**

the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as United States Application Number or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

# German Language Declaration

Ich beanspruche hiermit ausländische Prioritätsvorteile gemäß Title 35, US-Code, § 119 (a)-(d), bzw. § 365(b) aller unten aufgeführten Auslandsanmeldungen für Patente oder Erfinderurkunden, oder § 365(a) aller PCT internationalen Anmeldungen, welche wenigstens ein Land ausser den Vereinigten Staaten von Amerika benennen, und habe nachstehend durch ankreuzen sämtliche Auslands- anmeldungen für Patente bzw. Erfinderurkunden oder PCT internationale Anmeldungen angegeben, deren Anmeldetag dem der Anmeldung, für welche Priorität beansprucht wird, vorangeht.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications
(Frühere ausländische Anmeldungen)

| (Number) (Nummer) | (Country) (Land) | Priority Not Claimed (Priorität nicht beansprucht) |
|---|---|---|
| | Germany, DE | ☐ |
| (Day/Month/Year Filed) (Tag/Monat/Jahr der Anmeldung) | 198 28 450.6 | |
| | 26 June 1998 | |
| | | ☐ |
| (Day/Month/Year Filed) (Tag/Monat/Jahr der Anmeldung) | | |

Ich beanspruche hiermit Prioritätsvorteile unter Title 35, US-Code, § 119(e) aller US-Hilfsanmeldungen wie unten aufgezählt.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

| (Application No.) (Aktenzeichen) | (Filing Date) (Anmeldetag) |
|---|---|
| | |
| | |

Ich beanspruche hiermit die mir unter Title 35, US-Code, § 120 zustehenden Vorteile aller unten aufgeführten US-Patentanmeldungen bzw. § 365(c) aller PCT internationalen Anmeldungen, welche die Vereinigten Staaten von Amerika benennen, und erkenne, insofern der Gegenstand eines jeden früheren Anspruchs dieser Patentanmeldung nicht in einer US-Patentanmeldung, bzw. PCT internationalen Anmeldung in in einer gemäß dem ersten Absatz von Title 35, US-Code, § 112 vorgeschriebenen Art und Weise offenbart wurde, meine Pflicht zur Offenbarung jeglicher Informationen an, die zur Prüfung der Patentfähigkeit in Einklang mit Title 37, Code of Federal Regulations, § 1.56 von Belang sind und die im Zeitraum zwischen dem Anmeldetag der früheren Patentanmeldung und dem nationalen oder im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesen (PCT) gültigen internationalen Anmeldetags bekannt geworden sind

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

| (Application No.) (Aktenzeichen) | (Filing Date) (Anmeldetag) | (Status) (patented, pending, abandoned) (Status) (patentiert, schwebend, aufgegeben) |
|---|---|---|
| PCT/DE99/01844 | (pending) | |
| | | (Status) (patented, pending, abandoned) (Status) (patentiert, schwebend, aufgegeben) |

Ich erkläre hiermit, daß alle in der vorliegenden Erklärung von mir gemachten Angaben nach bestem Wissen und Gewissen der Wahrheit entsprechen, und ferner daß ich diese eidesstattliche Erklärung in Kenntnis dessen ablege, daß wissentlich und vorsätzlich falsche Angaben oder dergleichen gemäß § 1001, Title 18 des US-Code strafbar sind und mit Geldstrafe und/oder Gefängnis bestraft werden können und daß derartige wissentlich und vorsätzlich falsche Angaben die Rechtswirksamkeit der vorliegenden Patentanmeldung oder eines aufgrund deren erteilten Patentes gefährden können.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE


# German Language Declaration

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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

Haynes and Boone, LLP
Warren B. Kice

Postanschrift:

Send Correspondence to:

214/651-5634

Telefonische Auskünfte: *(Name und Telefonnummer)*

Direct Telephone Calls to: *(name and telephone number)*

| | |
|---|---|
| Vor- und Zuname des einzigen oder ersten Erfinders / DD | Full name of sole or first inventor<br>JOMAA, Hassan |
| Unterschrift des Erfinders Datum | Inventor's signature Date 11/12/2000 |
| Wohnsitz | Residence Breslauer Strasse 24<br>D-35398 Giessen, GERMANY DEX |
| Staatsangehörigkeit | Citizenship<br>German |
| Postanschrift | Post Office Address Breslauer Strasse 24<br>D-35398 Giessen, GERMANY |
| | |
| Vor- und Zuname des zweiten Miterfinders (falls zutreffend) | Full name of second joint inventor, if any |
| Unterschrift des zweiten Erfinders Datum | Second Inventor's signature Date |
| Wohnsitz | Residence |
| Staatsangehörigkeit | Citizenship |
| Postanschrift | Post Office Address |
| | |

(Im Falle dritter und weiterer Miterfinder sind die entsprechenden Informationen und Unterschriften hinzuzufügen.)

(Supply similar information and signature for third and subsequent joint inventors.)